(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number
WO 01/51462 A1

(51) International Patent Classification[7]: C07C 311/51, A61K 31/18, A61P 37/00, 29/00, 25/00, 35/00, 7/00, 41/00

(21) International Application Number: PCT/US01/01006

(22) International Filing Date: 10 January 2001 (10.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/482,813 13 January 2000 (13.01.2000) US

(71) Applicant *(for all designated States except US)*: **IDUN PHARMACEUTICALS, INC.** [US/US]; 9380 Judicial Drive, San Diego, CA 92121 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TERNANSKY, Robert, J.** [US/US]; 3469 Camino Valencia, Carlsbad, CA 92009 (US). **GLADSTONE, Patricia, L.** [CA/US]; 9242 Pebblestone Lane, San Diego, CA 92126 (US). **TOMASELLI, Kevin, J.** [US/US]; 3665 Jackdaw Street, San Diego, CA 92103 (US).

(74) Agents: **HERMANNS, Karl, R.** et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

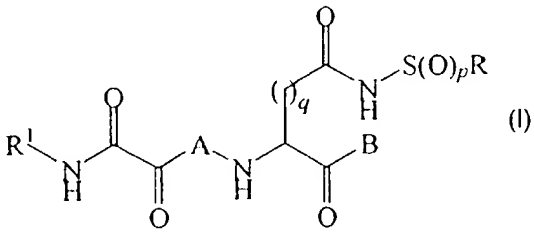
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF THE ICE/Ced-3 FAMILY OF CYSTEINE PROTEASES



(I)

(57) Abstract: This invention is directed to novel oxamyl dipeptide ICE/ced-3 family inhibitor compounds having the structure (I) wherein A, B, R, R^1, p and q are as defined herein. The invention is also directed to pharmaceutical compositions containing one or more of these compounds, as well as to the use of such compositions in the treatment of patients suffering inflammatory, autoimmune and neurodegenerative diseases, for the prevention of ischemic injury, and for the preservation of organs that are to undergo a transplantation procedure.

WO 01/51462 A1

INHIBITORS OF THE ICE/ced-3 FAMILY OF CYSTEINE PROTEASES

Technical Field

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme and related proteases ("ICE/ced-3 family of cysteine proteases"), as well as pharmaceutical compositions comprising these compounds and to methods of using such pharmaceutical compositions.

Background of the Invention

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al., Immunology Today, 7:45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response. Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84:4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19:1531-1536 (1989).

IL-1β is synthesized as a biologically inactive precursor, proIL-1β. ProIL-1β is cleaved by a cysteine protease called interleukin-1β converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R. et al., J. Biol. Chem., 265:14526-14528 (1992); A.D. Howard et al., J. Immunol., 147:2964-2969 (1991).

ICE is a cysteine protease localized primarily in monocytes. In addition to promoting the pro-inflammatory and immunoregulatory properties of IL-1β, ICE, and particularly its homologues, also appear to be involved in the regulation of cell death or apoptosis. Yuan, J. et al., Cell, 75:641-652 (1993); Miura, M. et al., Cell, 75:653-660 (1993); Nett-Giordalisi, M.A. et

al., J. Cell Biochem., 17B:117 (1993). In particular, ICE or ICE/ced-3 homologues are thought to be associated with the regulation of apoptosis in neurogenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259:760-762 (1993); Gagliardini, V. et al., Science, 263:826-828 (1994).

Thus, disease states in which inhibitors of the ICE/ced-3 family of cysteine proteases may be useful as therapeutic agents include: infectious diseases, such as meningitis and salpingitis; septic shock, respiratory diseases; inflammatory conditions, such as arthritis, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis and reperfusion injury, ischemic diseases such as the myocardial infarction, stroke and ischemic kidney disease; immune-based diseases, such as hypersensitivity; auto-immune diseases, such as multiple sclerosis; bone diseases; and certain neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Such inhibitors are also useful for the repopulation of hematopoietic cells following chemo- and radiation therapy and for prolonging organ viability for use in transplantation.

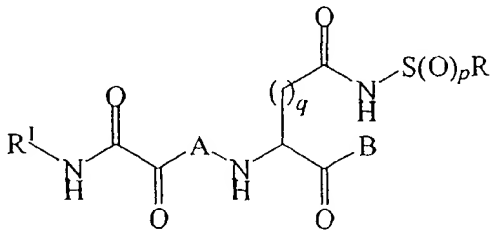
ICE/ced-3 inhibitors represent a class of compounds useful for the control of the above-listed disease states. Peptide and peptidyl inhibitors of ICE have been described. However, such inhibitors have been typically characterized by undesirable pharmacologic properties, such as poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. These undesirable properties have hampered their development into effective drugs.

Accordingly, the need exists for compounds that can effectively inhibit the action of the ICE/ced-3 family of proteases, for use as agents for preventing unwanted apoptosis, and for treating chronic and acute forms of IL-1 mediated diseases such as inflammatory, autoimmune or neurodegenerative diseases. The present invention satisfies this need and provides further related advantages.

Summary of the Invention

In general, the compounds of this invention incorporate a sulfonamido ($NHSO_2$) or sulfinamido (NHSO) modified (N-substituted)oxamyl group as a dipeptide mimetic. The resulting compounds exhibit improved properties relative to their peptidic counterparts, for example, such as improved cell penetration or improved absorption and metabolic stability resulting in enhanced bioavailability.

One aspect of the instant invention is the compounds of the following Formula I:



Formula I

wherein A, B, R, R^1, p and q are as defined below, as well as pharmaceutically acceptable salts thereof.

A further aspect of the instant invention is a pharmaceutical composition comprising a compound of the above Formula I and a pharmaceutically-acceptable carrier therefor.

Another aspect of this invention involves a method for treating an autoimmune disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

Yet another aspect of the instant invention is a method for treating an inflammatory disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

A further aspect of the instant invention is a method for treating a neurodegenerative disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

Another aspect of the instant invention is a method of preventing ischemic injury to a patient suffering from a disease associated with ischemic injury comprising administering an effective amount of the pharmaceutical composition discussed above to a patient in need of such treatment.

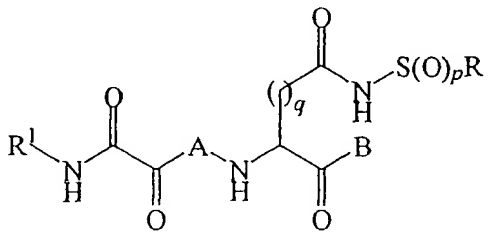
A further aspect of the instant invention is a method for expanding of hematopoietic cell populations and/or enhancing their survival by contacting the cells with an effective amount of the pharmaceutical composition discussed above. Cell populations included in the method of the invention include (but are not limited to) granulocytes, monocytes, erthrocytes, lymphocytes and platelets for use in cell transfusions.

An alternate aspect of the instant invention is a method of prolonging the viability of an organ that has been removed from the donor for the purpose of a future transplantation procedure, which comprises applying an effective amount of the pharmaceutical composition discussed above to the organ, thereby prolonging the viability of the organ as compared to an untreated organ. The organ may be an intact organ, or isolated cells derived from an organ (*e.g.*, isolated pancreatic islet cells, isolated dopaminergic neurons, blood or hematopoietic cells).

These and other aspects of this invention will be evident upon reference to the following detailed description.

Detailed Description of the Invention

As mentioned above, one aspect of the instant invention is the compounds of the Formula I:



Formula I

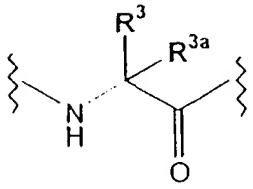
wherein:

p is 1 or 2;

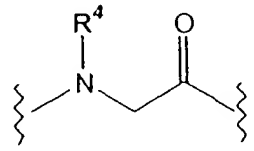
q is 1 or 2;

R and R^1 are the same or different and independently alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, substituted (heteroaryl)alkyl, $R^{1a}(R^{1b})N$ or $R^{1c}O$;

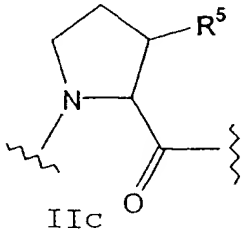
A is a natural or unnatural amino acid of Formula IIa-i:



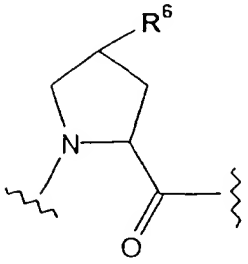
IIa



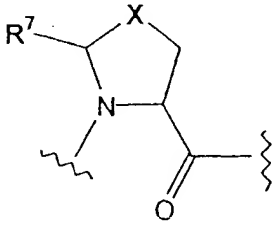
IIb



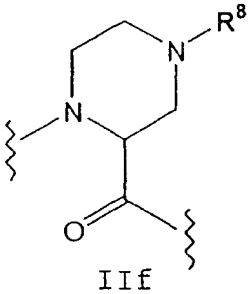
IIc



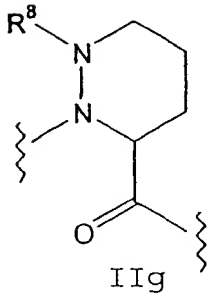
IId



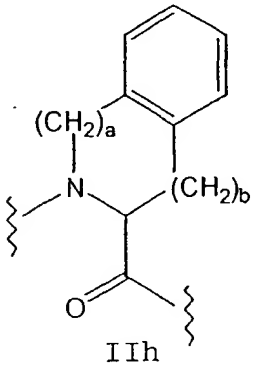
IIe



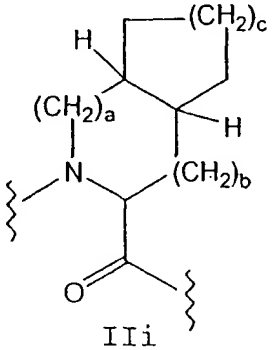
IIf



IIg

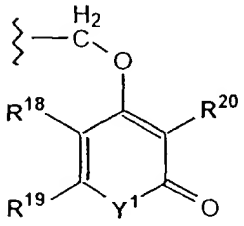


IIh

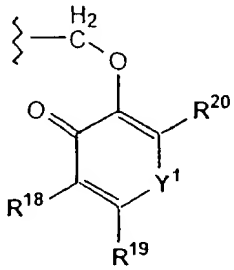


IIi

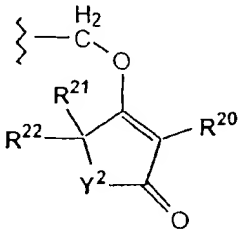
B is a hydrogen atom, a deuterium atom, alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, 2-benzoxazolyl, substituted 2-oxazolyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), $(CH_2)_n$(substituted 1 or 2-naphthyl), $(CH_2)_n$(heteroaryl), $(CH_2)_n$(substituted heteroaryl), halomethyl, CO_2R^{12}, $CONR^{13}R^{14}$, CH_2ZR^{15}, CH_2OCO(aryl), CH_2OCO(heteroaryl), or $CH_2OPO(R^{16})R^{17}$, where Z is an oxygen or a sulfur atom, or B is a group of the Formula IIIa-c:



IIIa



IIIb



IIIc

and wherein:

R^{1a} and R^{1b} are the same or different and, at each occurrence, independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, or substituted (heteroaryl)alkyl, with the proviso that R^{1a} and R^{1b} cannot both be hydrogen;

R^{1c} is, at each occurrrence, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, or substituted (heteroaryl)alkyl;

R^3 is C_{1-6} lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_nNH_2$, $(CH_2)_nNHCOR^9$, $(CH_2)_nN(C=NH)NH_2$, $(CH_2)_mCO_2R^2$, $(CH_2)_mOR^{10}$, $(CH_2)_mSR^{11}$, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl) or $(CH_2)_n$(heteroaryl), wherein heteroaryl includes pyridyl, thienyl, furyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyrazinyl, pyrimidyl, triazinyl, tetrazolyl, and indolyl;

R^{3a} is hydrogen or methyl, or R^3 and R^{3a} taken together are $-(CH_2)_d-$ where d is an interger from 2 to 6;

R^4 is phenyl, substituted phenyl, $(CH_2)_m$phenyl, $(CH_2)_m$(substituted phenyl), cycloalkyl, or benzofused cycloalkyl;

R^5 is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^6 is hydrogen, fluorine, oxo, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), OR^{10}, SR^{11} or $NHCOR^9$;

R^7 is hydrogen, oxo (*i.e.*, = O), lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^8 is lower alkyl, cycloalkyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), or COR^9;

R^9 is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), OR^{12}, or $NR^{13}R^{14}$;

R^{10} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{11} is lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{12} is lower alkyl, cycloalkyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{13} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{14} is hydrogen or lower alkyl;

or R^{13} and R^{14} taken together form a five to seven membered carbocyclic or heterocyclic ring, such as morpholine, or N-substituted piperazine;

R^{15} is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), or $(CH_2)_n$(heteroaryl);

R^{16} and R^{17} are independently lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, phenylalkyl, substituted phenylalkyl, or (cycloalkyl)alkyl;

R^{18} and R^{19} are independently hydrogen, alkyl, phenyl, substituted phenyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or R^{18} and R^{19} taken together are $-(CH=CH)_2-$;

R^{20} is hydrogen, alkyl, phenyl, substituted phenyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl);

R^{21}, R^{22} and R^{23} are independently hydrogen, or alkyl;

X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or S;

Y^1 is O or NR^{23};

Y^2 is CH_2, O, or NR^{23};

a is 0 or 1 and b is 1 or 2, provided that when a is 1 then b is 1;

c is 1 or 2, provided that when c is 1 then a is 0 and b is 1;

m is 1 or 2; and

n is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

As used herein, the term "alkyl" means a straight or branched C_1 to C_{10} carbon chain, such as methyl, ethyl, tert-butyl, iso-propyl, n-octyl, and the like. The term "lower alkyl" means a straight chain or branched C_1 to C_6 carbon chain, such as methyl, ethyl, iso-propyl, and the like.

The term "cycloalkyl" means a mono-, bi-, or tricyclic ring that is either fully saturated or partially unsaturated. Examples of such a ring include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, cis- or trans decalin, bicyclo[2.2.1]hept-2-ene, cyclohex-1-enyl, cyclopent-1-enyl, 1,4-cyclooctadienyl, and the like.

The term "(cycloalkyl)alkyl" means the above-defined alkyl group substituted with one of the above cycloalkyl rings. Examples of such a group include (cyclohexyl)methyl, 3-(cyclopropyl)-n-propyl, 5-(cyclopentyl)hexyl, 6-(adamantyl)hexyl, and the like.

The term "substituted phenyl" specifies a phenyl group substituted with one or more substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, trifluoromethyl, alkyl, alkoxy, acyl, acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(lower alkyl)carboxamide, protected N-(lower alkyl)carboxamide, N,N-di(lower alkyl)carboxamide, N-((lower alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or by a substituted or unsubstituted phenyl group, such that in the latter case a biphenyl or naphthyl group results, or wherein two adjacent alkyl substituents on the substituted phenyl ring taken together form a cycloalkyl to yield, for example, tetrahydronaphthyl or indanyl.

Examples of the term "substituted phenyl" includes a mono-, di-, tri-, tetra- or penta(halo)phenyl group such as 2-, 3- or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2-,3- or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-, 3- or 4-fluorophenyl, 2,4,6-trifluorophenyl, 2,3,5,6-tetrafluorophenyl, 2,3,4,5-tetrafluorophenyl, 2,3,4,5,6-pentafluorophenyl, and the like; a mono or di(hydroxy)phenyl group such as 2-, 3-, or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2-, 3-, or 4-nitrophenyl; a cyanophenyl group, for example, 2-,3- or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2-, 3-, or 4-methylphenyl, 2,4-dimethylphenyl, 2-, 3- or 4-(iso-propyl)phenyl, 2-, 3-, or 4-ethylphenyl, 2-, 3- or 4-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 2,6-dimethoxyphenyl, 2-, 3- or 4-(iso-propoxy)phenyl, 2-, 3- or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2-, 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2-, 3- or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2-, 3- or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-, 3- or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like.

The term "phenylalkyl" means one of the above phenyl groups attached to one of the above-described alkyl groups, and the term "substituted phenylalkyl" means that either the phenyl or the alkyl, or both, are substituted with one or more of the above-defined substituents. Examples of such groups include 2-phenyl-1-chloroethyl, 2-(4'-methoxyphenyl)ethyl, 4-(2',6'-dihydroxy phenyl)n-hexyl, 2-(5'-cyano-3'-methoxyphenyl)n-pentyl, 3-(2',6'-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4'-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4'-

aminomethylphenyl)-3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl, (4-hydroxynapth-2-yl)methyl, and the like.

The term "substituted naphthyl" means a naphthyl group sustituted with one or more of the above-identified subtituents, and the term "(1 or 2 naphthyl)alkyl" means a naphthyl (1 or 2) attached to one of the above-described alkyl groups.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo groups. These terms may also be used to describe one or more halogens, which are the same or different. Preferred halogens in the context of this invention are chloro and fluoro.

The term "aryl" refers to aromatic five and six membered carbocyclic rings. Six membered rings are preferred.

The term "heteroaryl" denotes optionally substituted aromatic five-membered or six-membered heterocyclic rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen atoms, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms.

The following ring systems are representative examples of the heterocyclic radicals denoted by the term "heteroaryl" (whether substituted or unsubstituted): thienyl, furyl, pyrrolyl, pyrrolidinyl, imidazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, triazinyl, thiadiazinyl tetrazolo, 1,5-[b]pyridazinyl and purinyl, as well as benzo-fused derivatives, for example, benzoxazolyl, benzothiazolyl, benzimidazolyl and indolyl.

Substituents for the above optionally substituted heteroaryl rings are from one to three halo, trihalomethyl, amino, protected amino, amino salts, mono-substituted amino, di-substituted amino, carboxy, protected carboxy, carboxylate salts, hydroxy, protected hydroxy, salts of a hydroxy group, lower alkoxy, lower alkylthio, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, (cycloalkyl)alkyl, substituted (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, and substituted phenylalkyl groups.

Substituents for the heteroaryl group are as defined above, or as set forth below. As used in conjunction with the above substituents for heteroaryl rings, "trihalomethyl" can be

trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl, "lower alkoxy" means a C_1 to C_4 alkoxy group, similarly, "lower alkylthio" means a C_1 to C_4 alkylthio group. The term "substituted lower alkyl" means the above-defined lower alkyl group substituted from one to three times by a hydroxy, protected hydroxy, amino, protected amino, cyano, halo, trifluoromethyl, mono-substituted amino, di-substituted amino, lower alkoxy, lower alkylthio, carboxy, protected carboxy, or a carboxy, amino, and/or hydroxy salt.

As used in conjunction with the substituents for the heteroaryl rings, the terms "substituted (cycloalkyl)alkyl" and "substituted cycloalkyl" are as defined above substituted with the same groups as listed for a "substituted alkyl" group. The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the group consisting of phenyl, substituted phenyl, alkyl, substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 alkynyl, C_7 to C_{16} alkylaryl, C_7 to C_{16} substituted alkylaryl and heteroaryl group. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino." The term "(disubstituted)amino" refers to amino groups with two substituents chosen from the group consisting of phenyl, substituted phenyl, alkyl, substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_7 to C_{16} alkylaryl, C_7 to C_{16} substituted alkylaryl and heteroaryl. The two substituents can be the same or different. The term "heteroaryl(alkyl)" denotes an alkyl group as defined above, substituted at any position by a heteroaryl group, as above defined.

Furthermore, the above optionally substituted five-membered or six-membered heterocyclic rings, and the above cycloalky rings, can optionally be fused to a aromatic 5-membered or 6-membered aryl or heteroaryl ring system. For example, the rings can be optionally fused to an aromatic 5-membered or 6-membered ring system such as a pyridine or a triazole system, and preferably to a benzene ring.

The term "pharmaceutically-acceptable salt" encompasses those salts that form with the carboxylate anions and includes salts formed with the organic and inorganic cations such as those chosen from the alkali and alkaline earth metals, (for example, lithium, sodium, potassium, magnesium, barium and calcium); and ammonium ion; and the organic cations (for

example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzyl-ammonium, dibenzylethylenediammonium, and like cations.) Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine, and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. A preferred cation for the carboxylate anion is the sodium cation. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and includes organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and the like acids.

The compounds of Formula I may also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include t-butyl, benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylpropyl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β-(trimethylsilyl)ethyl, β-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-propenyl and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these

groups are found in C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl (THP), 2-methoxyprop-2-yl, 1-ethoxyeth-1-yl, methoxymethyl, β-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl, and the like.

Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3. A preferred hydroxy-protecting group is the tetrahydropyranyl (THP) group. The related term "protected hydroxy" denotes a hydroxy group bonded to one of the above hydroxy-protecting groups.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom.

Examples of such amino-protecting groups include the formyl ("For") group, the trityl group, the phthalimido group, the trichloroacetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type protecting groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenylyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-oxycarbonyl, 1,1-diphenylpropyl-1-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl

("Ddz"), 2-(*p*-toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyl-oxycarbonyl, cyclohexanyloxy-carbonyl, 1-methyl-cyclohexanyloxy-carbonyl, 2-methylcyclohexanyl-oxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluorenyl-methoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyl-oxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyl-oxycarbonyl ("Cbz"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, α-2,4,5,-tetramethylbenzyl-oxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyl-oxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxy-carbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxy-carbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxy-carbonyl and the like; the benzoylmethylsulfonyl group, the 2,2,5,7,8-pentamethylchroman-6-sulfonyl group ("PMC"), the dithiasuccinoyl ("Dts") group, the 2-(nitro)phenyl-sulfenyl group ("Nps"), the diphenylphosphine oxide group, and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Preferred amino-protecting groups are Boc, Cbz and Fmoc. Further examples of amino-protecting groups embraced by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised Ed., Springer-Verlag, New York, NY, 1984 and 1993, and J.M. Stewart and J.D. Young, "Solid Phase Peptide Synthesis," 2nd Ed., Pierce Chemical Co., Rockford, IL, 1984, E. Atherton and R.C. Shephard, "Solid Phase Peptide Synthesis - A Practical Approach" IRL Press, Oxford, England (1989), each of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The terms "natural and unnatural amino acid" refers to both the naturally occurring amino acids and other non-proteinogenic α-amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ-carboxyglutamic acid, arginine, ornithine and lysine. Examples of unnatural alpha-amino acids include hydroxylysine, citrulline, kynurenine, (4-aminophenyl)alanine, 3-(2'-naphthyl)alanine, 3-(1'-naphthyl)alanine, methionine sulfone, (t-butyl)alanine, (t-butyl)glycine, 4-hydroxyphenyl-glycine, aminoalanine, phenylglycine, vinylalanine, propargyl-gylcine, 1,2,4-triazolo-3-alanine, thyronine, 6-hydroxytryptophan, 5-hydroxytryptophan, 3-hydroxy-kynurenine, 3-aminotyrosine, trifluoromethylalanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)cysteine, 3,4-dimethoxy-phenylalanine, 3-(2'-thiazolyl)alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-(trifluoromethylphenyl)alanine, (cyclohexyl)glycine, thiohistidine, 3-methoxytyrosine, norleucine, norvaline, alloisoleucine, homoarginine, thioproline, dehydro-proline, hydroxyproline, homoproline, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, α-amino-n-butyric acid, cyclohexylalanine, 2-amino-3-phenylbutyric acid, phenylalanine substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following groups: a (C_1 to C_4)alkyl, a (C_1 to C_4)alkoxy, a halogen or a nitro group, or substituted once with a methylenedioxy group; β-2- and 3-thienylalanine; β-2- and 3-furanylalanine; β-2-, 3- and 4-pyridylalanine; β-(benzothienyl-2- and 3-yl)alanine; β-(1- and 2-naphthyl)alanine; O-alkylated derivatives of serine, threonine or tyrosine; S-alkylated cysteine, S-alkylated homocysteine, the O-sulfate, O-phosphate and O-carboxylate esters of tyrosine; 3-(sulfo)tyrosine, 3-(carboxy)tyrosine, 3-(phospho)tyrosine, the 4-methane-sulfonic acid ester of tyrosine, 4-methanephosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitrotyrosine, ε-alkyllysine, and delta-alkyl ornithine. Any of these α-amino acids may be substituted with a methyl group at the alpha position, a halogen at any position of the aromatic residue on the α-amino side chain, or an

appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are discussed above.

The compounds of this invention may be modified by appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (*e.g.*, blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of exertion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Some examples of pro-drug forms include ketal, acetal, oxime, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the group donated as "A" in Formula I or the modified aspartic acid residue attached to the group denoted as "A".

With regard to the *p* and *q* groups of Forumula I, typical embodiments include compounds wherein *q* is 1 and *p* is 2.

Compounds of this invention with respect to the R and R^1 groups in Formula I, include those wherein:

R is lower alkyl; and

R^1 is phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, heteroaryl, or (heteroaryl)alkyl.

More typically, the compounds of this invention with respect to the R and R^1 groups include those wherein:

R is methyl; and

R^1 is phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, or (1 or 2 naphthyl)alkyl.

Compounds of this invention with respect to the A group in Formula I, include those of Formula IIa wherein:

R^3 is lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_nNH_2$, $(CH_2)_mOR^{10}$, $(CH_2)_mSR^{11}$, $(CH_2)_n$cycloalkyl,$(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{3a} is hydrogen;

R^{10} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{11} is lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl); and

n = 1-4 and m = 1 or 2.

Compounds of this invention with respect to the A group in Formula I also include those of Formula IIb wherein:

R^4 is phenyl, substituted phenyl, $(CH_2)_m$phenyl, $(CH_2)_m$(substituted phenyl), cycloalkyl, or 2-indanyl; and

m = 1 or 2.

Another group of compounds with respect to the A group in Formula I include those of Formula IId wherein:

R^6 is hydrogen, fluorine, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), OR^{10}, or SR^{11};

R^{10} and R^{11} are independently cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl); and

n = 1-4.

A fourth group of compounds with respect to the A group in Formula I include those of Formula IIe wherein:

R^7 is hydrogen, oxo, cycloalkyl, phenyl, substituted phenyl, or naphthyl; and

X = CH_2, $(CH_2)_2$, $(CH_2)_3$, or S.

Another group of compounds with respect to the A group in Formula I include those of Formula IIh wherein:

a = 0 and b = 1 or 2.

Compounds of this invention with respect to the B group in Formula I include those wherein:

B is hydrogen, 2-benzoxazolyl, substituted 2-oxazolyl, CH_2ZR^{15}, CH_2OCO(aryl), or $CH_2OPO(R^{16})R^{17}$, where Z is an oxygen or a sulfur atom;

R^{15} is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), or $(CH_2)_n$(heteroaryl); and

R^{16} and R^{17} are independently alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, phenylalkyl, substituted phenylalkyl, or (cycloalkyl)alkyl.

Another group of compounds with respect to the B group in Formula I include those of Formula IIIa-c wherein:

Y^1 is O or NR^{23};

Y^2 is CH_2, O, or NR^{23};

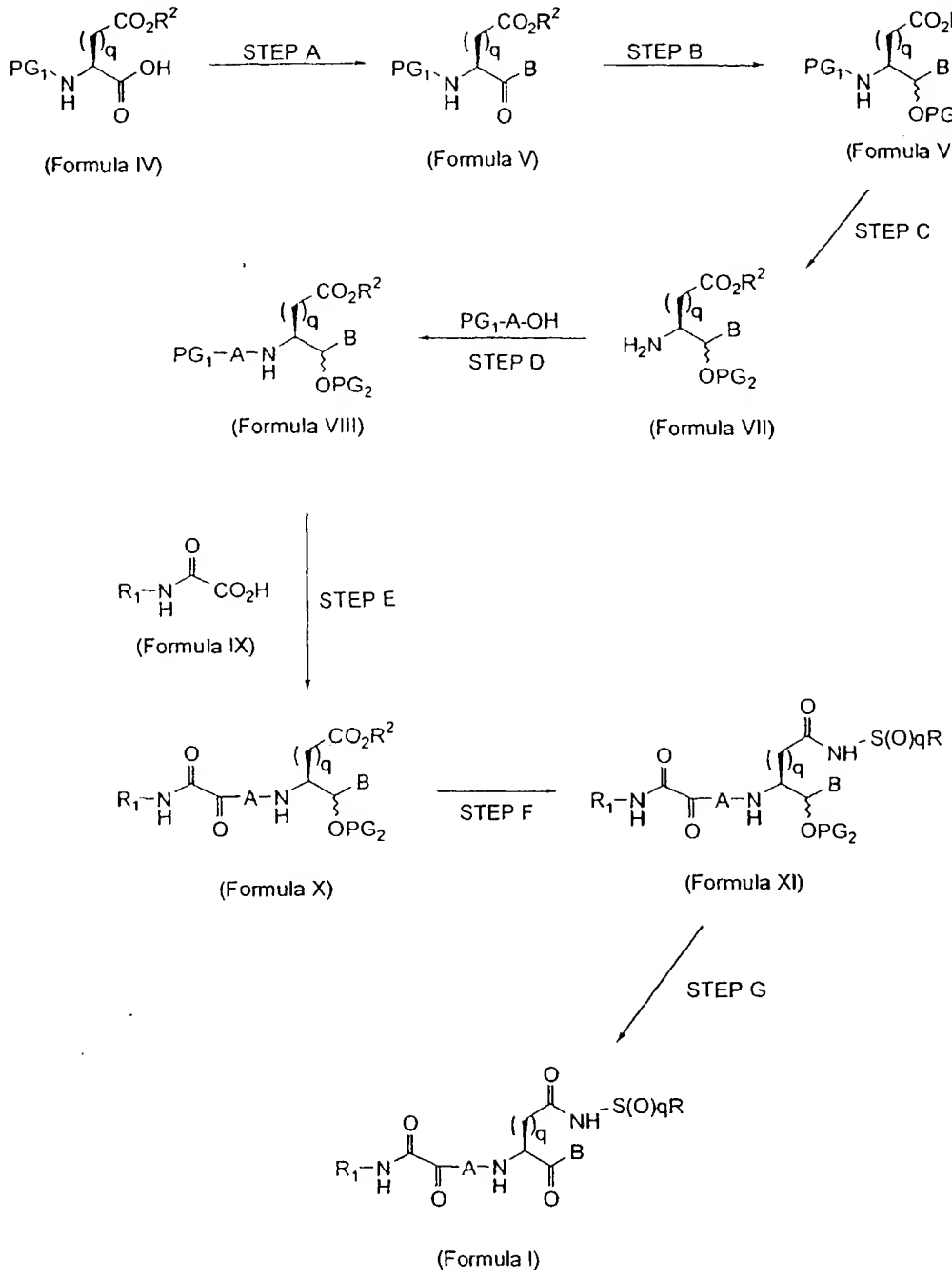
R^{18} and R^{19} are independently hydrogen, alkyl, or phenyl, or R^{18} and R^{19} taken together are -(CH=CH)$_2$-;

R^{20} is hydrogen, alkyl, phenyl, substituted phenyl, $(CH_2)_n$phenyl, or $(CH_2)_n$(substituted phenyl); and

R^{21}, R^{22} and R^{23} are independently hydrogen or alkyl.

The compounds of Formula I may be synthesized using conventional techniques, as well as by the following Reaction Scheme. To that end, in the following Reaction Scheme, *q* is 1, and corresponding compounds wherein *q* is 2 may be made in the same manner by employing the corresponding ethylene (-CH_2CH_2-) starting material in place of the methylene (-CH_2-) moiety.

Reaction Scheme



In the above Scheme 1, R^2 represents hydrogen or a carboxy protecting group, wherein the carboxy protecting group is as defined above. "PG_1" stands for an amino protecting group, "PG_2" stands for a hydroxy-protecting group, and "A" stands for a natural or unnatural amino acid of formula IIa through IIi, as discussed above.

The modified aspartic acids of Formula V can be prepared by methods well known in the art. See, for example, European Patent Application 519,748; PCT Patent Application No. PCT/EP92/02472; PCT Patent Application No. PCT/US91/06595; PCT Patent Application No. PCT/US91/02339; European Patent Application No. 623,592; World Patent Application No. WO 93/09135; PCT Patent Application No. PCT/US94/08868; European Patent Application No. 623,606; European Patent Application No. 618,223; European Patent Application No. 533,226; European Patent Application No. 528,487; European Patent Application No. 618,233; PCT Patent Application No. PCT/EP92/02472; World Patent Application No. WO 93/09135; PCT Patent Application No. PCT/US93/03589; and PCT Patent Application No. PCT/US93/00481, all of which are herein incorporated by reference. For example, in Step A, the carboxylic acid moiety of Formula IV is converted to its bromomethyl ketone which is then treated with either $R^{15}Z$-H, (aryl)-CO_2H, (heteroaryl)-CO_2H, or $R^{16}(R^{17})PO_2H$ in the presence of an inorganic base such as potassium carbonate or potassium fluoride in an inert solvent such as dimethyl formamide to give the corresponding intermediate of Formula V in which B is CH_2ZR^{15}, CH_2OCO(aryl), CH_2OCO(heteroaryl), or $CH_2OPO(R^{16})R^{17}$, respectively.

Reduction of the carbonyl group in Formula V (Step B) with a hydride reducing agent such as sodium borohydride gives rise to a diastereomeric mixture of alcohols which are further protected with a hydroxy-protecting group (PG_2) as referenced above.

The coupling reaction carried out under Step D is performed in the presence of a standard peptide coupling agent such as the combination of the combination of dicyclohexylcarbodiimide(DCC) and 1-hydroxy-benzotriazole(HOBt), as well as the BOP (benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate) reagent, pyBOP (benzotriazolyloxy-tris(N-pyrolidinyl)phosphoniumhexafluorophosphate), HATU (O-7-Azabenzotriazol-1-yl-tetramethylisouronium-hexafluorophosphate), HBTU (O-benzotriazolyly-

tetramethylisouronium-hexafluorophosphate), and EEDQ (1-ethyloxycarbonyl-2-ethyloxy-1,2-dihydroquinoline) reagents, the combination of 1-ethyl(3,3'-dimethyl-1'-aminopropyl)carbodiimide (EDAC) and HOBt, and the like, as discussed in J. Jones, "Amino Acid and Peptide Synthesis," Steven G. Davis ed., Oxford University Press, Oxford, pp. 25-41 (1992); M. Bodanzky, "Principles of Peptide Synthesis," Hafner et al. ed., Springer-Verlag, Berlin Heidelberg, pp. 9-52 and pp. 202-251 (1984); M. Bodanzky, "Peptide Chemistry, A Practical Textbook," Springer-Verlag, Berlin Heidelberg, pp. 55-73 and pp. 129-180; and Stewart and Young, "Solid Phase Peptide Synthesis," Pierce Chemical Company, (1984), all of which are herein incorporated by reference. The amino protecting group is then removed and the resulting amine is coupled to the (N-substituted) oxamic acid of Formula IX (Step E). Again, this coupling reaction uses the standard peptide coupling reactions mentioned above.

Conversion of the carboxylate of Formula X to the sulfonimide (Step F) involves removal of the carboxy protecting group (R_2) using standard conditions well known in the art. The resulting carboxylic acid is then treated with CDI (2 eq.) in THF at room temperature for 3 hours, followed by $H_2NS(O)_yR$ (2 eq.) in DBU (2 eq.) at room temperature for 4 hours.

The sulfonimide intermediate of Formula XI is reacted in Step G with TsOH (0.4 eq.) in methanol at room temperature for 30 minutes to de-protect the alcohol , which may be converted to the corresponding carbonyl of Formula I by employing the Dess-Martin periodinane reagent and DCM at room temperature for 30 minutes.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle (hereinafter collectively referred to as "pharmaceutically-acceptable carriers"). Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchange, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin; buffer substances such as the various phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids; water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium

chloride, and zinc salts; colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyarylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat, and the like.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or by an implanted reservoir. Oral and parenteral administration are preferred. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carrier which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in capsule form useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with

emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible to topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-applied transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The compounds of this invention may be used in combination with either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of cytokines other than IL-1β.

The compounds of this invention can also be administered in combination with immunomodulators (*e.g.*, bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexons and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical compositions according to this invention may be comprised of a combination of a compound of Formula I and another therapeutic or prophylactic agent mentioned above.

The disease states which may be treated or prevented by the instant pharmaceutical compositions include, but are not limited to, inflammatory diseases, autoimmune diseases and neurodegenerative diseases, and for inhibiting unwanted apoptosis involved in ischemic injury, such as ischemic injury to the heart (*e.g.*, myocardial infarction), brain (*e.g.*, stroke), and kidney (*e.g.*, ischemic kidney disease). As a consequence of their ability to inhibit apoptosis, the present pharmaceutical compositions are also useful for the repopulation of hematopoietic cells of a patient following chemotherapy. Methods of administering an effective amount of the above-described pharmaceutical compositions to mammals, also referred to herein as patients, in need of such treatment (that is, those suffering from inflammatory diseases, autoimmune diseases, neurodegenerative diseases and for the repopulation of hematopoietic cells in cancer patients who have undergone chemotherapy) are another aspect of the instant invention. Finally, as a further consequence of their ability to inhibit apoptosis, the instant pharmaceutical compositions may be used in a method to prolong the viability of organs to be used in transplantations.

Inflammatory disease which may be treated or prevented include, for example, septic shock, septicemia, and adult respiratory distress syndrome. Target autoimmune diseases include, for example, rheumatoid, arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus,

autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis and multiple sclerosis. Target neurodegenerative diseases include, for example, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and primary lateral sclerosis. The pharmaceutical compositions of this invention may also be used to promote wound healing. Target diseases associated with harmful, apoptosis, in other words, those associated with ischemic injury, includes myocardial infarction, stroke, and ischemic kidney disease. The pharmaceutical compositions of this invention may also be used to treat infectious diseases, especially those involved with viral infections.

The term "effective amount" refers to dosage levels of the order of from about 0.05 milligrams to about 140 milligrams per kilogram of body weight per day for use in the treatment of the above-indicated conditions (typically about 2.5 milligrams to about 7 grams per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 milligrams of the compound per kilogram of body weight per day (about 0.5 milligrams to about 3.5 grams per patient per day).

The amount of the compounds of Formula I that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 milligrams to 5 grams of a compound of Formula I combined with an appropriate and convenient amount of a pharmaceutically-acceptable carrier which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 milligram to about 500 milligrams of an active compound of Formula I.

It will be understood, however, that the specific "effective amount" for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing prevention or therapy.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to the ICE/ced-3 family of cysteine protease or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

In the following Examples, proton NMR spectra were obtained at 300 MHz; chemical shifts are quoted downfield from internal tetramethylsilane.

EXAMPLE 1

Assay for Inhibition of ICE/ced-3 Protease Family Activity

A. Determination of IC_{50} Values

Fluorescence enzyme assays detecting the activity of the compounds of Formula I utilizing the recombinant ICE and CPP32 enzymes are performed essentially according to Thornberry et al. (Nature, 356:768:774 (1992)) and Nicholson et al. (Nature, 376:37-43 (1995)) respectively, (herein incorporated by reference) in 96 well microtiter plates. The substrate is Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC) for the ICE assay and Acetyl-Asp-Glu-Val-Asp-amino-4-methylcoumarin for the CPP32, Mch2, Mch3 and Mch5 assays. Enzyme reactions are run in ICE buffer (25 mM HEPES, 1 mM EDTA, 0.1% CHAPS, 10% sucrose, pH

7.5) containing 2 mM DTT at room temperature in duplicate. The assays are performed by mixing the following components:

50 µL ICE, Mch2, Mch5, CPP32 (18.8, 38, 8.1 and 0.153 nM concentrations, respectively) or Mch3 (1 unit) enzyme in ICE buffer containing either 8.0 (ICE, Mch2, Mch3, CPP32) or 20 (Mch5) mM DTT;

50 µL compound of Formula I or ICE buffer (control); and

100 µL of 20 µM substrate.

The enzyme and the compound of Formula I to be assayed are allowed to preincubate in the microtitre plate wells for 30 minutes at room temperature prior to the addition of substrate to initiate the reaction. Fluorescent AMC product formation is monitored for one hour at room temperature by measuring the fluorescence emission at 460 nm using an excitation wavelength of 360 nm. The fluorescence change in duplicate (control) wells are averaged and the mean values are plotted as a function of inhibitor concentration to determine the inhibitor concentration producing 50% inhibition (IC_{50}).

B. Determination of the dissociation constant Ki and irreversible rate constant k_3 for irreversible inhibitors

For the irreversible inhibition of a ICE/ced-3 Family Protease enzyme with a competitive irreversible inhibitor; using the model represented by the following formulas:

$$E + I \underset{}{\overset{K_i}{\rightleftharpoons}} EI \overset{k_3}{\dashrightarrow} E\text{-}I$$

$$E + S \underset{}{\overset{K_s}{\rightleftharpoons}} ES \overset{k_s}{\dashrightarrow} E + S$$

The product formation at time t may be expressed as:

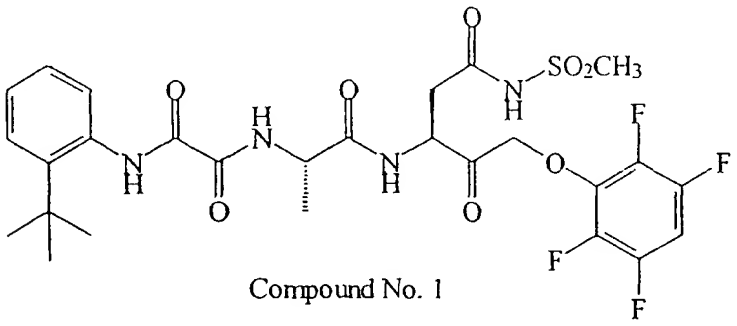
$$[P]_t = [E]^T \left(\frac{[S]K_i}{[I]K_s}\right)\left(\frac{k_s}{k_3}\right)\left[1\text{-}e^{-k_3 t/(1+\frac{K_i}{[I]}(1+\frac{[S]}{K_s}))}\right]$$

Equation 1

where E, I, EI and E-I denote the active enzyme, inhibitor, non-covalent enzyme-inhibitor complex and covalent enzyme-inhibitor adduct, respectively. The K_i value is the overall dissociation constant of the reversible binding steps, and k_3 is the irreversible rate constant. The [S] and K_s values are the substate concentration and dissociation constant of the substrate bound to the enzyme, respectively. $[E]^T$ is the total enzyme concentration.

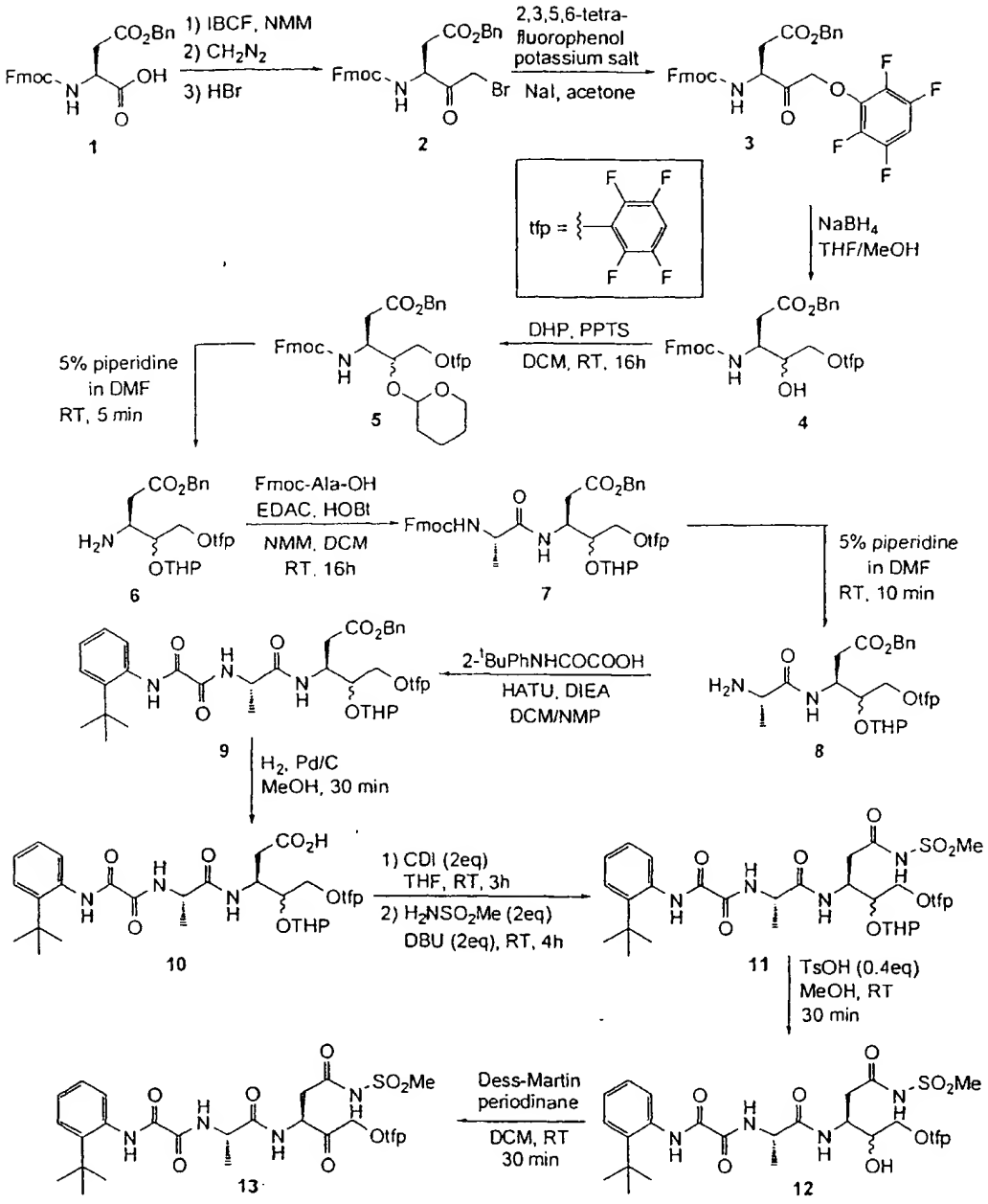
EXAMPLE 2

3S)-N -Methanesulfonyl-3-[N-(N'-(2-t-Butylphenyl)Oxamyl)Valinyl] Amino-5-(2',3',5',6'-Tetrafluorophenoxy)-4-Oxapentanamide



Compound No. 1

Compound No. 1 was made according to the following reaction scheme, the procedures for which are set forth below.


1) IBCF, NMM
2) CH2N2
3) HBr
2,3,5,6-tetra-fluorophenol potassium salt
NaI, acetone
tfp =
NaBH4
THF/MeOH
DHP, PPTS
DCM, RT, 16h
5% piperidine in DMF RT, 5 min
Fmoc-Ala-OH
EDAC, HOBt
NMM, DCM
RT, 16h
5% piperidine in DMF
RT, 10 min
2-tBuPhNHCOCOOH
HATU, DIEA
DCM/NMP
H2, Pd/C
MeOH, 30 min
1) CDI (2eq)
THF, RT, 3h
2) H2NSO2Me (2eq)
DBU (2eq), RT, 4h
TsOH (0.4eq)
MeOH, RT
30 min
Dess-Martin periodinane
DCM, RT
30 min

Bromomethylketone 2:

4-Methylmorpholine (0.76 mL, 6.9 mmol) was added to a solution of Fmoc-Asp(OBn)-OH (1) (2.05 g, 4.62 mmol) in 50 mL of dry THF at –10oC under an atmosphere of nitrogen, followed by the addition of isobutyl chloroformate (0.90 mL, 6.9 mmol), and the solution was stirred for 20 minutes. The resulting white precipitate was removed by filtration and the filtrate was cooled to 0oC. In a separate flask, 1-methyl-3-nitro-1-nitrosoguanidine (1.10 g, 7.44 mmol) was added to a vigorously stirred mixture of diethyl ether (14 mL) and 40% KOH (8 mL) at 0oC. The resulting mixture was stirred for 10 minutes and the layers were allowed to separate. The ether layer was transferred via plastic pipette to the mixed anhydride in THF and the reaction mixture was stirred for 30 minutes. Then, 48% HBr in water (2.10 mL) was added and the reaction mixture was warmed to room temperature over 15 minutes. The solution was diluted with ethyl acetate, washed twice with saturated aqueous sodium bicarbonate, once with brine, dried (MgSO4), and concentrated. The resulting crude product was purified by flash chromatography on silica gel, eluting with 35% ethyl acetate-hexanes, to afford 1.70 g (71%) of 2 as a white solid. 1H-NMR (300 MHz, CDCl3): d 7.77 (d, J=8 Hz, 2H), 7.58 (d, J=8 Hz, 2H), 7.45-7.29 (m, 9H), 5.77 (d, J=9 Hz, 1H), 5.12 (s, 2H), 4.79-4.71 (m, 1H), 4.63-4.42 (m, 2H), 4.21 (t, J=6 Hz, 1H), 4.04 (s, 2H), 2.97 (ABXq, J=17, 5 Hz, 2H).

Ketone 3:

Sodium iodide (205 mg, 1.37 mmol) was added to a solution of 2 (3.39 g, 6.49 mmol) in 20 mL of acetone at room temperature, followed by the addition of the potassium salt of 2,3,5,6-tetrafluorophenol (1.39 g, 6.82 mmol) and the resulting mixture was stirred for one hour. The reaction mixture was diluted with ethyl acetate, washed twice with brine, dried (MgSO4), and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with 1:1:3 dichloromethane/diethyl ether/hexanes, to provide 3.32 g (84%) of 3 as a white solid. 1H-NMR (300 MHz, CDCl3): d 7.76 (d, J=8 Hz, 2H), 7.58 (d, J=8Hz, 2H), 7.44-7.27 (m, 9H), 6.85-6.73 (m, 1H), 5.73 (d, J=9 Hz, 1H), 5.15-4.92 (m, 4H), 4.75-4.67 (m, 1H), 4.61-4.42 (m, 2H), 4.21 (t, J=6 Hz, 1H), 3.00 (ABXq, J=18, 4 Hz, 2H).

Alcohol 4:

Sodium borohydride (248 mg, 6.56 mmol) was added to a solution of 3 (608 mg, 5.43 mmol) in 14 mL of dry methanol and 14 mL of dry THF at 0 ºC and the resulting mixture was stirred for 30 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted three times with dichloromethane, and the combined dichloromethane layers were washed once with brine, dried (MgSO4), and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate-hexanes, to give 2.43 g (73%) of 4 as a white solid. 1H-NMR (300 MHz, CDCl3): d 7.78-7.74 (m, 2H), 7.57 (d, J=7 Hz, 2H), 7.44-7.27 (m, 9H), 6.87-6.75 (m, 1H), 5.62 (d, J=9 Hz, 0.3H), 5.44 (d, J=9 Hz, 0.2H), 5.29-5.23 (m, 0.5H), 5.16-5.11 (m, 1H), 4.69 (d, J=6 Hz, 1H), 4.59-4.37 (m, 4H), 4.30-4.04 (m, 3H), 3.35-3.09 (m, 1H), 2.94-2.41 (m, 2H).

THP Ether 5:

3,4-Dihydro-2H-pyran (0.55 mL, 6.0 mmol) and pyridinium p-toluenesulfonate (218 mg, 0.866 mmol) were added to a solution of 4 (2.43 g, 3.99 mmol) in 20 mL of dry dichloromethane and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed twice with saturated aqueous sodium bicarbonate solution, once with brine, dried (MgSO4), and concentrated. The crude product was purified by flash chromatography on silica gel, first eluting with 15% ethyl acetate-hexanes and then with 50% ethyl acetate-hexanes, to afford 1.71 g (62%) of 5 as a colorless oil. 1H-NMR (300 MHz, CDCl3): d 7.76 (d, J=7 Hz, 2H), 7.62-7.55 (m, 2H), 7.42-7.27 (m, 9H), 6.84-6.71 (m, 1H), 6.21 (d, J=9 Hz, 0.3H), 5.65 (d, J=9 Hz, 0.2H), 5.33-5.27 (m, 0.5H), 5.13 (t, J=3 Hz, 2H), 4.72-4.04 (m, 8H), 3.91-3.73 (m, 1H), 3.51-3.36 (m, 1H), 2.98-2.57 (m, 2H), 1.86-1.61 (m, 2H), 1.57-1.43 (m, 4H).

Amine 6:

Piperidine (0.75 mL, 7.6 mmol) was added to a solution of 5 (1.70 g, 2.45 mmol) in 15 mL of dry DMF at room temperature and the resulting solution was stirred for 5 minutes.

The reaction mixture was diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, twice with water, once with brine, dried (MgSO4), and concentrated. The crude product was purified by flash chromatography on silica gel, first eluting with 50% ethyl acetate-hexanes and then with 80% ethyl acetate-hexanes, to provide 793 mg (69%) of 6 as a colorless oil. 1H-NMR (300 MHz, CDCl3): d 7.39-7.29 (m, 5H), 6.82-6.70 (m, 1H), 5.15 (s, 2H), 4.78-4.63 (m, 1H), 4.53-4.26 (m, 2H), 4.03-3.79 (m, 2H), 3.71-3.43 (m, 2H), 2.80-2.43 (m, 2H), 1.85-1.66 (m, 2H), 1.57-1.45 (m, 4H).

Dipeptide 7:

Amine 6 (790 mg, 1.68 mmol) and Fmoc-Ala-OH (578 mg, 1.86 mmol) were dissolved in 40 mL of dry dichloromethane. 1-Hydroxybenzotriazole hydrate (342 mg, 2.53 mmol) was added to this solution, followed by the addition of 4-methylmorpholine (0.30 mL, 2.7 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (391 mg, 2.04 mmol), and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, once with saturated aqueous sodium bicarbonate solution, once with brine, dried (MgSO4), and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with 40% ethyl acetate-hexanes, to give 1.17 g (91%) of 7 as a white solid. 1H-NMR (300 MHz, CDCl3): d 7.76 (d, J=7 Hz, 2H), 7.62-7.55 (m, 2H), 7.40 (t, J=7 Hz, 2H), 7.35-7.28 (m, 7H), 6.95-6.46 (m, 2H), 5.45-5.25 (m, 1H), 5.11-5.05 (m, 2H), 4.75-4.30 (m, 5H), 4.28-4.04 (m, 4H), 3.94-3.76 (m, 1H), 3.50-3.36 (m, 1H), 2.95-2.61 (m, 2H), 1.82-1.65 (m, 2H), 1.54-1.41 (m, 4H), 1.39-1.32 (m, 3H).

Amine 8:

Piperidine (0.50 mL, 5.1 mmol) was added to a solution of 7 (1.17 g, 1.53 mmol) in 10 mL of dry DMF at room temperature and the resulting solution was stirred for 10 minutes. The reaction mixture was diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, twice with water, once with brine, dried (MgSO4), and concentrated.

The crude product was purified by flash chromatography on silica gel, first eluting with 50% ethyl acetate-hexanes and then with 20% methanol-dichloromethane, to provide 806 mg (97%) of 8 as a yellow oil. 1H-NMR (300 MHz, CDCl3): d 8.01 (d, J=9 Hz, 0.35H), 7.93 (d, J=9 Hz, 0.24H), 7.64 (d, J=9 Hz, 0.17H), 7.56 (d, J=9Hz, 0.24H), 7.38-7.28 (m, 5H), 6.83-6.70 (m, 1H), 5.17-5.06 (m, 2H), 4.76-4.24 (m, 4H), 4.23-4.03 (m, 1H), 3.91-3.79 (m, 1H), 3.51-3.38 (m, 2H), 2.95-2.61 (m, 2H), 1.85-1.66 (m, 2H), 1.59-1.41 (m, 4H), 1.29-1.25 (m, 3H).

Oxamide 9:

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (308 mg, 0.809 mmol) was added to 2-t-butylphenyloxamic acid (150 mg, 0.678 mmol) in 0.75 mL of dry NMP and 1.5 mL of dry dichloromethane at room temperature. The mixture was stirred for 15 minutes, and then a solution of 8 (365 mg, 0.672 mmol) in 1.5 mL of dry dichloromethane was added, followed by the addition of diisopropylethyl amine (0.35 mL, 2.0 mmol). The reaction mixture was stirred for 14 hours, diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, once with saturated aqueous sodium bicarbonate solution, once with brine, dried (MgSO4), and concentrated. The crude product was purified by flash chromatography, eluting with 35% ethyl acetate-hexanes, to give 315 mg (63%) of 9 as a colorless oil. 1H-NMR (300 MHz, CDCl3): d 9.57 (s, 0.4H), 9.54 (s, 0.6H), 8.11-7.95 (m, 2H), 7.44-7.24 (m, 7H), 7.21-7.13 (m, 1H), 6.96-6.50 (m, 2H), 5.13-5.07 (m, 2H), 4.77-4.05 (m, 6H), 3.97-3.77 (m, 1H), 3.55-3.39 (m, 1H), 2.96-2.62 (m, 2H), 1.85-1.61 (m, 2H), 1.55-1.37 (m, 16H).

Acid 10:

10% Palladium on carbon (76 mg) was added to a solution of 9 (300 mg, 0.402 mmol) in anhydrous methanol (7 mL) under an atmosphere of nitrogen and the flask was then evacuated with the house vacuum. The mixture was stirred under a balloon of hydrogen gas for 30 minutes, then filtered through Celite, and eluted with methanol. The solution was concentrated to afford 249 mg (94%) of 10 as a white solid.

Methyl sulfonimide 11:

1,1'-Carbonyldiimidazole (124 mg, 0.766 mmol) was added to a solution of 10 (249 mg, 0.380 mmol) in dry THF (6 mL) under an atmosphere of nitrogen, and the reaction mixture was stirred for 3 hours. The mixture was cooled to 0oC, and the methanesulfonamide (73 mg, 0.77 mmol) was added, followed by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.115 mL, 0.77 mmol). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate, washed once with 1 N HCl solution, twice with water, once with brine, dried (MgSO4), and concentrated. The residue was reconcentrated from dichloromethane to provide 271 mg (97%) of 11 as a white solid. 1H-NMR (300 MHz, CDCl3): d 9.59-9.48 (m, 1H), 8.25-8.15 (m, 1H), 7.95-7.88 (m, 1H), 7.69 (d, J=8 Hz, 0.3H), 7.44-7.38 (m, 1H), 7.28-7.13 (m, 2.4H), 6.93-6.87 (m, 0.3H), 6.85-6.71 (m, 1H), 4.75-4.33 (m, 4H), 4.27-4.01 (m, 3H), 3.87-3.43 (m, 1H), 3.28-3.23 (m, 3H), 2.93-2.56 (m, 2H), 1.86-1.68 (m, 2H), 1.55-1.39 (m, 16H).

Alcohol 12:

p-Toluenesulfonic acid (21 mg, 0.11 mmol) was added to a solution of 11 (202 mg, 0.275 mmol) in anhydrous methanol (3 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate, washed three times with water, once with brine, dried (MgSO4), and concentrated to afford 166 mg (93%) of 12 as a white solid. 1H-NMR (300 MHz, CDCl3): d 9.57-9.46 (m, 1H), 8.34 (t, J=8 Hz, 1H), 7.80 (d, J=8 Hz, 1H), 7.44-7.30 (m, 2H), 7.23-7.12 (m, 2H), 6.83-6.69 (m, 1H), 4.66-4.45 (m, 3H), 4.33-4.10 (m, 3H), 3.26 (s, 1.2H), 3.25 (s, 1.8H), 2.90-2.76 (m, 2H), 1.48-1.38 (m, 12H).

Methylsulfonimide 13 ("Compound No. 1"):

Dess-Martin periodinane (126 mg, 0.297 mmol) was added to a solution of 12 (154 mg, 0.238 mmol) in 5 mL of dry dichloromethane, and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate, washed twice with water, once with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash

chromatography, eluting first with 60% ethyl acetate-hexanes and then with 80% ethyl acetate-hexanes, to provide 114 mg (74%) of **13** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 8.27-7.87 (m, 2H), 7.42 (d, *J*=8 Hz, 1H), 7.29-7.15 (m, 2H), 6.92-6.77 (m, 2H), 5.02-4.77 (m, 3H), 4.56-4.27 (m, 2H), 3.37 (s, 3H), 3.06-2.60 (m, 2H), 1.56-1.42 (m, 12H); MS (ESI) *m/e* 645 [(M+)−1].

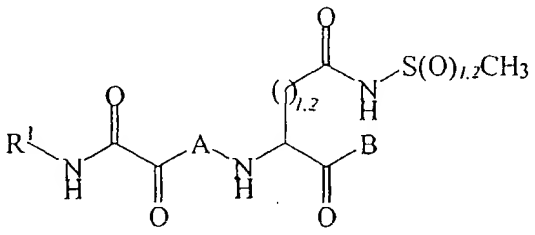
EXAMPLE 3

Representative Compounds

The representative compounds listed in the following Table 1 may be made according to the procedures set forth in Example 2.

Table 1

Representative Compounds



Cpd	A	B	R^1
1	NHCH($CH_2CH(CH_3)_2$)CO	H	1-naphthyl
2	NHCH($CH_2CH(CH_3)_2$)CO	CH_2F	1-naphthyl
3	NHCH($CH(CH_3)_2$)CO	CH_2F	1-naphthyl
4	NHCH($CH(CH_3)_2$)CO	CH_2OCO(2,4-diCl-Ph)	1-naphthyl
5	NHCH($CH(CH_3)_2$)CO	CH_2O(2,6-diF-Ph)	1-naphthyl

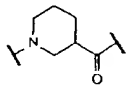
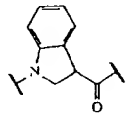
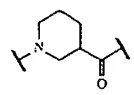
6	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,4,6-triF-Ph)	1-naphthyl
7	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	1-naphthyl
8	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(6-Me-2-pyron-4-yl)	1-naphthyl
9	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2-Ph-5,6-benzopyran-4-on-3-yl)	1-naphthyl
10	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$OPO(Me)Ph	1-naphthyl
11	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$OPOPh$_2$	1-naphthyl
12	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2-CF$_3$-pyrimidin-4-yl)	1-naphthyl
13	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(5-CO$_2$Me-isoxazol-3-yl)	1-naphthyl
14	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$OPO(Me)(1-naphthyl)	1-naphthyl
15	NHCH(CH$_2$CH(CH$_3$)$_2$)CO	CH$_2$OPOPh$_2$	1-naphthyl
16	NHCH(CH$_2$CH(CH$_3$)$_2$)CO	CH$_2$OCO(2,6-diCl-Ph)	1-naphthyl
17	NHCH(CH$_2$CH(CH$_3$)$_2$)CO	CH$_2$O(2,4,6-triF-Ph)	1-naphthyl
18	NHCH(CH$_2$CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	1-naphthyl
19	NHCH(CH$_2$CH(CH$_3$)$_2$)CO	CH$_2$OPO(Me)Ph	1-naphthyl
20	NHCH(CH$_3$)CO	CH$_2$O(2-F-Ph)	(2-Ph)Ph
21	NHCH(CH$_3$)CO	CH$_2$OCO(2,6-di-Cl-Ph)	(2-Ph)Ph
22	NHCH(CH$_3$)CO	CH$_2$OPOPh$_2$	(2-Ph)Ph
23	NHCH(CH$_3$)CO	CH$_2$O(2-F-Ph)	(2-t-Bu)Ph
24	NHCH(CH$_3$)CO	CH$_2$OPOPh$_2$	(2-t-Bu)Ph

25	$NHCH(CH_3)CO$	$CH_2OCO(2,3,5,6\text{-tetra-Cl-Ph})$	1-naphthyl-CH_2
26	$NHCH(CH_3)CO$	$CH_2OCO(2,6\text{-di-Cl-Ph})$	1-naphthyl-CH_2
27	$NHCH(CH_3)CO$	CH_2OPOPh_2	1-naphthyl-CH_2
28	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	1-naphthyl-CH_2
29	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	$PhCH_2$
30	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	$Ph(CH_2)_2$
31	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	Ph_2CH
32	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	Ph
33	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	(2-Ph)Ph
34	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	$(2\text{-}PhCH_2)Ph$
35	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	(3-PhO)Ph
36	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	4-Cl-1-naphthyl
37	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	2-anthryl
38	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	2-benzimidazolyl
39	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	1-adamantanyl
40	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	(2-F)Ph
41	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	(4-F)Ph
42	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	$(2\text{-}CF_3)Ph$
43	$NHCH(CH(CH_3)_2)CO$	$CH_2O(2,3,5,6\text{-tetraF-Ph})$	(2-t-Bu)Ph

44	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(4-n-heptyl)Ph
45	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2-CH$_3$O)Ph
46	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2-PhO)Ph
47	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	2-naphthyl
48	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	5,6,7,8-tetrahydro-1-naphthyl
49	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	1-anthryl
50	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	2-pyridinyl
51	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	4-pyridinyl
52	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	2,3,5,6-tetrafluoro-4-pyridinyl
53	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	2-pyrazinyl
54	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	1,2,3,4-tetrahydro-1-naphthyl
55	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2-Cl)Ph
56	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2-Br)Ph
57	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2-I)Ph
58	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2,6-di-F)Ph
59	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(2,5-di-t-Bu)Ph
60	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	5-indanyl
61	NHCH(CH(CH$_3$)$_2$)CO	CH$_2$O(2,3,5,6-tetraF-Ph)	(3,4,5-tri-MeO)PhCH$_2$

62	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	methyl
63	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	*n*-heptyl
64	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	t-octyl
65	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	cyclo-hexyl
66	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	5-Ph-3-pyrazolyl
67	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-F-4-I)Ph
68	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2,3,4,5-tetra-F)Ph
69	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2,3,4,6-tetra-F)Ph
70	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2,3,5,6-tetra-Cl)Ph
71	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2,3,4,5,6-penta-F)Ph
72	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	Ph_2N
73	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	$PHCH_2$(Ph)N
74	NHCH(CH(CH_3)$_2$)CO	CH_2O(2,3,5,6-tetraF-Ph)	$PhCH_2O$
75	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-t-Bu)Ph
76	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-CF_3)Ph
77	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-Ph)Ph
78	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-$PhCH_2$)Ph
79	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-PhO)Ph
80	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(3-PhO)Ph

81	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	5,6,7,8-tetrahydro-1-naphthyl
82	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	1-naphthyl
83	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	Ph
84	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2,6-di-F)Ph
85	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(4-Ph)Ph
86	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	(4-MeO)Ph
87	NHCH(CH_3)CO	CH_2O(2,3,5,6-tetraF-Ph)	Ph_2CH
88	NHCH(CH_2cyclohexyl)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-PhO)Ph
89	NHCH(CH_2cyclohexyl)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-Ph)Ph
90	NHCH(CH_2cyclohexyl)CO	CH_2O(2,3,5,6-tetraF-Ph)	(2-$PhCH_2$)Ph
91	NHCH(CH_2cyclohexyl)CO	CH_2O(2,3,5,6-tetraF-Ph)	1-naphthyl
92	NHCH(CH_2cyclohexyl)CO	CH_2OCO(2,6-diCl-Ph)	5,6,7,8-tetrahydro-1-naphthyl
93	NHCH(CH_2cyclohexyl)CO	CH_2O(2,3,5,6-tetra-F-Ph)	5,6,7,8-tetrahydro-1-naphthyl
94	NHCH(CH_2cyclohexyl)CO	CH_2OPO(Me)Ph	5,6,7,8-tetrahydro-1-naphthyl
95	NHCH(CH_2cyclohexyl)CO	CH_2OPOPh_2	5,6,7,8-tetrahydro-1-naphthyl
96	NHCH(CH_2cyclohexyl)CO	CH_2OPO(Me)Ph	(2-$PhCH_2$)Ph
97	NHCH(CH_2cyclohexyl)CO	CH_2OPOPh_2	(2-$PhCH_2$)Ph

98	NHCH(CH_2cyclohexyl)CO	$CH_2OPO(Me)Ph$	(2-Ph)Ph
99	NHCH(CH_2cyclohexyl)CO	CH_2OPOPh_2	(2-Ph)Ph
100		CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
101		CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
102	NHCH(cyclohexyl)CO	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
103	norleucine	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
104	(t-butyl)glycine	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
105	(t-butyl)alanine	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
106	phenylglycine	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
107	phenylalanine	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
108	homophenylalanine	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
109	1-aminocyclopentane carboxylic acid	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
110	NHCH($CH_2CH_2SOCH_3$)CO	CH_2O(2,3,5,6-tetra-F-Ph)	1-naphthyl
111		H	1-naphthyl
112	NHCH($CH(CH_3)_2$)CO	H	2-(1H-tetrazol-5-yl)Ph
113	NHCH($CH(CH_3)_2$)CO	H	1-adamantanyl

114	NHCH(CH(CH_3)$_2$)CO	H	Ph
115	NHCH(CH(CH_3)$_2$)CO	H	$PhCH_2$
116	NHCH(CH(CH_3)$_2$)CO	H	$Ph(CH_2)_2$
117	NHCH(CH(CH_3)$_2$)CO	H	(2-CF_3)Ph
118	NHCH(CH(CH_3)$_2$)CO	H	(2-t-Bu)Ph
119	NHCH(CH(CH_3)$_2$)CO	H	(2-Ph)Ph
120	NHCH(CH(CH_3)$_2$)CO	H	(2-$PhCH_2$)Ph
121	NHCH(CH(CH_3)$_2$)CO	H	(2-PhO)Ph
122	NHCH(CH(CH_3)$_2$)CO	H	2-naphthyl
123	NHCH(CH(CH_3)$_2$)CO	H	1-naphthyl
124	NHCH(CH(CH_3)$_2$)CO	H	4-Cl-1-naphthyl
125	NHCH(CH(CH_3)$_2$)CO	H	5,6,7,8-tetrahydro-1-naphthyl
126	NHCH(CH(CH_3)$_2$)CO	H	1,2,3,4-tetrahydro-1-naphthyl
127	NHCH(CH(CH_3)$_2$)CO	H	(1-naphthyl)CH_2

EXAMPLE 4

Activity of Representative Compound

The activity of a representative compound of this invention (*i.e.*, Compound No. 1) was evaluated according to the procedures disclosed in Example 1. More specifically, the equations set forth in Example 1 were used determine the K_i values of inhibitor (*i.e.*, Compound

No. 1) bound to a ICE/ced-3 family protease. A continuous assay was run for sixty minutes at various concentrations of the inhibitor and the substrate. The assay was formulated essentially the same as described in Example 1, except that the reaction was initiated by adding the enzyme to the substrate-inhibitor mixture. The K_i values were obtained by simulating the product AMC formation as a function of time according to Equation 1. The results of this assay are set forth below in Table 1, wherein the reference compound was Cbz-ValAlaAsp-CH_2F

Table 2

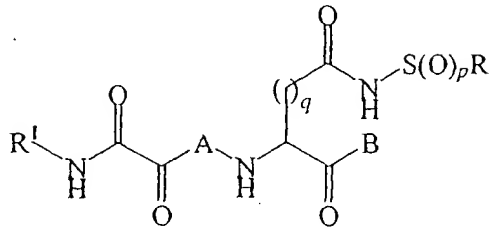
Cpd. No.	mICE K_i (μM)	CPP32 K_i (μM)	MCH-2 K_i (μM))	MCH-5 K_i (μM)
1	0.004	0.856	0.681	0.011
reference	0.015	0.820	0.594	0.018

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.

CLAIMS

We claim:

1. A compound of the following formula:



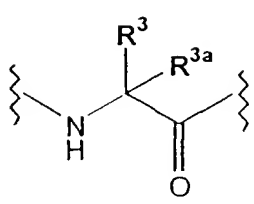
wherein:

p is 1 or 2;

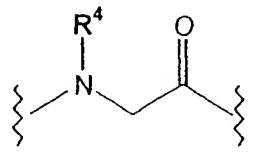
q is 1 or 2;

R and R^1 are the same or different and independently alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, substituted (heteroaryl)alkyl, $R^{1a}(R^{1b})N$ or $R^{1c}O$;

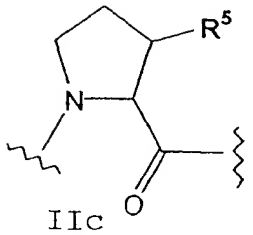
A is a natural or unnatural amino acid of Formula IIa-i:



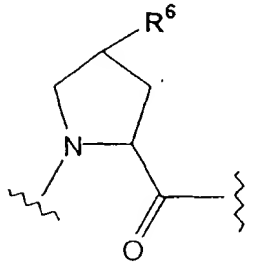
IIa



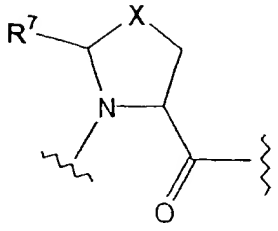
IIb



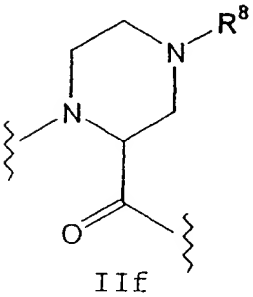
IIc



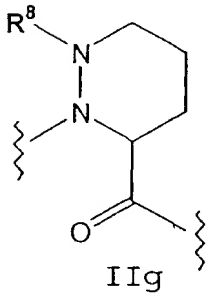
IId



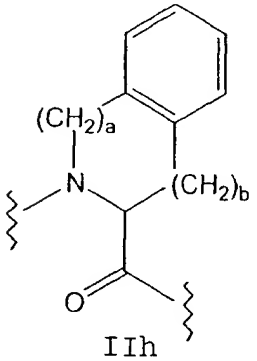
IIe



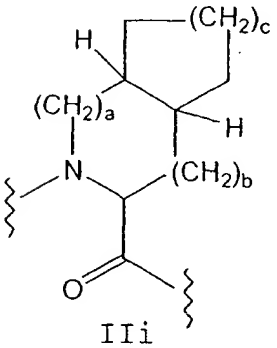
IIf



IIg

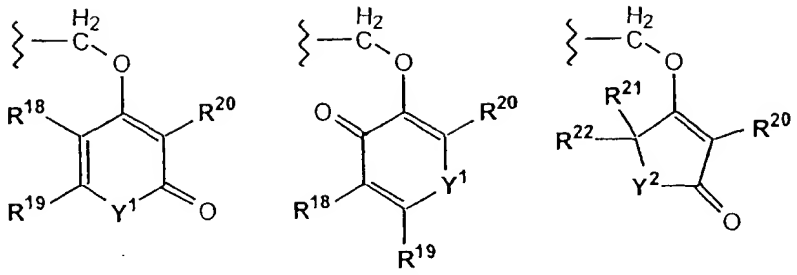


IIh



IIi

B is a hydrogen atom, a deuterium atom, alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, 2-benzoxazolyl, substituted 2-oxazolyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), $(CH_2)_n$(substituted 1 or 2-naphthyl), $(CH_2)_n$(heteroaryl), $(CH_2)_n$(substituted heteroaryl), halomethyl, CO_2R^{12}, $CONR^{13}R^{14}$, CH_2ZR^{15}, CH_2OCO(aryl), CH_2OCO(heteroaryl), or $CH_2OPO(R^{16})R^{17}$, where Z is an oxygen or a sulfur atom, or B is a group of the Formula IIIa-c:



IIIa IIIb IIIc

and wherein:

R^{1a} and R^{1b} are the same or different and, at each occurrence, independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, or substituted (heteroaryl)alkyl, with the proviso that R^{1a} and R^{1b} cannot both be hydrogen;

R^{1c} is, at each occurrrence, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, or substituted (heteroaryl)alkyl;

R^3 is C_{1-6} lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_nNH_2$, $(CH_2)_nNHCOR^9$, $(CH_2)_nN(C=NH)NH_2$, $(CH_2)_mCO_2R^2$, $(CH_2)_mOR^{10}$, $(CH_2)_mSR^{11}$, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl) or $(CH_2)_n$(heteroaryl), wherein heteroaryl includes pyridyl, thienyl, furyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyrazinyl, pyrimidyl, triazinyl, tetrazolyl, and indolyl;

R^{3a} is hydrogen or methyl, or R^3 and R^{3a} taken together are $-(CH_2)_d-$ where d is an interger from 2 to 6;

R^4 is phenyl, substituted phenyl, $(CH_2)_m$phenyl, $(CH_2)_m$(substituted phenyl), cycloalkyl, or benzofused cycloalkyl;

R^5 is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^6 is hydrogen, fluorine, oxo, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), OR^{10}, SR^{11} or $NHCOR^9$;

R^7 is hydrogen, oxo (*i.e.*, = O), lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^8 is lower alkyl, cycloalkyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), or COR^9;

R^9 is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), OR^{12}, or $NR^{13}R^{14}$;

R^{10} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{11} is lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl; $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{12} is lower alkyl, cycloalkyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{13} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl);

R^{14} is hydrogen or lower alkyl;

or R^{13} and R^{14} taken together form a five to seven membered carbocyclic or heterocyclic ring, such as morpholine, or N-substituted piperazine;

R^{15} is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), or $(CH_2)_n$(heteroaryl);

R^{16} and R^{17} are independently lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, phenylalkyl, substituted phenylalkyl, or (cycloalkyl)alkyl;

R^{18} and R^{19} are independently hydrogen, alkyl, phenyl, substituted phenyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or R^{18} and R^{19} taken together are $-(CH=CH)_2-$;

R^{20} is hydrogen, alkyl, phenyl, substituted phenyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl);

R^{21}, R^{22} and R^{23} are independently hydrogen, or alkyl;

X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or S;

Y^1 is O or NR^{25};

Y^2 is CH_2, O, or NR^{25};

a is 0 or 1 and b is 1 or 2, provided that when a is 1 then b is 1;

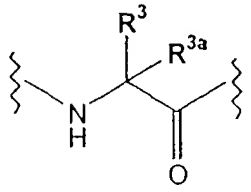
c is 1 or 2, provided that when c is 1 then a is 0 and b is 1;

m is 1 or 2; and

n is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein A is



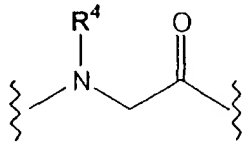
IIa

3. The compound of claim 2 wherein

R^3 is lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_nNH_2$, $(CH_2)_mOR^{10}$, $(CH_2)_mSR^{11}$, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), or $(CH_2)_n$(1 or 2-naphthyl); and

R^{3a} is hydrogen.

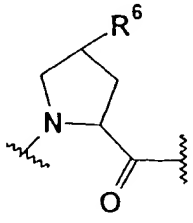
4. The compound of claim 1 wherein A is



IIb

5. The compound of claim 4 wherein R^4 is phenyl, substituted phenyl, $(CH_2)_m$phenyl, $(CH_2)_m$(substituted phenyl), cycloalkyl, or 2-indanyl.

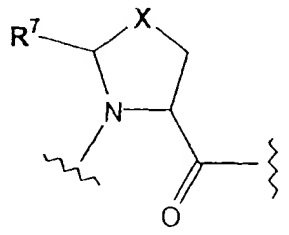
6. The compound of claim 1 wherein A is



IId

7. The compound of claim 6 wherein R^6 is hydrogen, fluorine, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$cycloalkyl, $(CH_2)_n$phenyl, $(CH_2)_n$(substituted phenyl), $(CH_2)_n$(1 or 2-naphthyl), OR^{10}, or SR^{11}.

8. The compound of claim 1 wherein A is



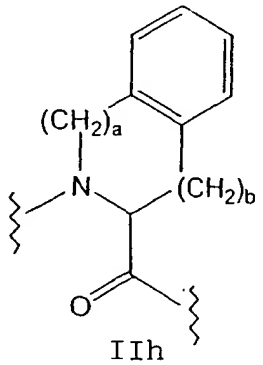
IIe

9. The compound of claim 8 wherein

R^7 is hydrogen, oxo, cycloalkyl, phenyl, substituted phenyl, or naphthyl; and

X = CH_2, $(CH_2)_2$, $(CH_2)_3$, or S.

10. The compound of claim 1 wherein A is

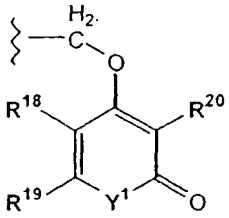


IIh

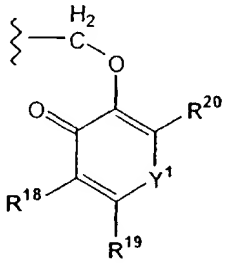
11. The compound of claim 10 wherein a is 0.

12. The compound of claim 1 wherein B is hydrogen, 2-benzoxazolyl, substituted 2-oxazolyl, CH_2ZR^{15}, CH_2OCO(aryl), or $CH_2OPO(R^{16})R^{17}$, and wherein Z is an oxygen or a sulfur atom.

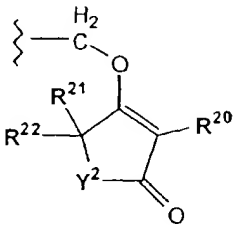
13. The compound of claim 1 wherein B is



IIIa



IIIb



IIIc

14. The compound of claim 13 wherein R^{18} and R^{19} are independently hydrogen, alkyl, or phenyl, or wherein R^{18} and R^{19} taken together are $-(CH=CH)_2-$.

15. The compound of claim 1 wherein R^1 is phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, heteroaryl, or (heteroaryl)alkyl.

16. The compound of claim 3 wherein R^3 is methyl, isopropyl, isobutyl, cyclohexylmethyl, t-butyl, cyclohexyl or phenyl.

17. The compound of claim 16 wherein B is CH_2O(2,3,5,6-tetrafluorophenyl).

18. The compound of claim 1 wherein R^1 is 1-naphthyl and A is valine.

19. The compound of claim 1 wherein R^1 is 1-naphthyl and B is CH_2O(2,3,5,6-tetrafluorophenyl).

20. The compound of claim 1 wherein R is lower alkyl.

21. The compound of claim 1 wherein R is methyl.

22. The compound of claim 1 wherein q is 1.

23. The compound of claim 1 wherein p is 2.

24. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

25. A method for treating an autoimmune disease, comprising administering an effective amount of the pharmaceutical composition of claim 24 to a patient in need thereof.

26. A method of treating an inflammatory disease, comprising administering an effective amount of the pharmaceutical composition of claim 24 to a patient in need thereof.

27. A method of treating a neurodegenerative disease, comprising administering an effective amount of the pharmaceutical composition of claim 24 to a patient in need thereof.

28. A method of preventing ischemic injury to a patient suffering from a disease associated with ischemic injury, comprising administering an effective amount of the pharmaceutical composition of claim 24 to a patient in need thereof.

29. A method for expanding of hematopoietic cell populations or enhancing their survival, comprising contacting the cells with an effective amount of the pharmaceutical composition of claim 24.

30. The method of claim 29 wherein the cell populations are granulocytes, monocytes, erthrocytes, lymphocytes or platelets for use in cell transfusions.

31. A method of prolonging the viability of an organ that has been removed from a donor or isolated cells derived from an organ for the purpose of a future transplantation procedure, comprising applying an effective amount of the pharmaceutical composition of claim

24 to the organ or isolated cells to prolong the viability of the same as compared to untreated organ or isolated cells.

32. The method of claim 31 wherein the organ is an intact organ.

33. The method of claim 31 wherein the isolated cells are pancreatic islet cells, dopaminergic neurons, blood cells, or hematopoietic cells.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 01/01006

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/51 A61K31/18 A61P37/00 A61P29/00 A61P25/00
A61P35/00 A61P7/00 A61P41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 11, 30 September 1999 (1999-09-30) -& JP 11 147873 A (YAMANOUCHI PHARMACEUTICAL), 2 June 1999 (1999-06-02) abstract	1-29
P,Y	WO 00 01666 A (IDUN PHARMACEUTICALS) 13 January 2000 (2000-01-13) page 1 -page 8; claims 1-29; example 75	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2001	31/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna ial Application No
PCT/US 01/01006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 11147873 A	02-06-1999	NONE	
WO 0001666 A	13-01-2000	US 6197750 B	06-03-2001
		AU 4856999 A	24-01-2000
		EP 1091930 A	18-04-2001
		NO 20006544 A	28-02-2001